REMARKS

Claims 1, 4, 7, and 18-26 are pending in the application. Claims 2, 3, 5, 6, and 8-17 have been cancelled without prejudice. Claims 1, 4, and 7 have been amended, and new claims 18-26 have been added. Support for the amendments and new claims can be found in original claims 2, 3, 5, 6, and 8 and in the specification at, e.g., page 4, lines 5-29. These amendments add no new matter.

35 U.S.C. § 112, Second Paragraph (Indefiniteness)

At page 2 of the Office Action, claim 7 was rejected as allegedly indefinite in its use of the term "candidate." Claim 7 has been amended to add the word "agent" following "candidate" in the first step of the method to recite a "candidate agent." In view of this amendment, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 103(a) (Obviousness)

At pages 3-6 of the Office Action, claims 1-8 were rejected as allegedly unpatentable over Birnbaumer et al. (U.S. Patent No. 5,932,417; referred to herein as "Birnbaumer") in view of Levy et al. (Am. J. Med. 1994 96:260-73; referred to herein as "Levy") and Draznin et al. (J. Biol. Chem. 1987 262(30):14385-88; referred to herein as "Draznin").

Applicants respectfully traverse the rejection in view of the claim amendments and the following remarks.

The currently claimed invention is based, at least in part, upon the inventors' surprising discovery that inhibition of "store-mediated" Ca^{2+} entry (SMCE) results in a decrease in insulin-stimulated glucose uptake in skeletal muscle. This finding supports a physiological role of SMCE and Ca^{2+} alterations in insulin action in skeletal muscle, where an increase in Ca^{2+} entry results in an increased insulin-mediated glucose uptake. As amended, the claims are directed to methods for identifying compounds that increase SMCE as agents that increase cellular glucose uptake.

Birnbaumer, the primary reference cited in the present obviousness rejection, describes human "transient receptor potential" (trp) proteins and methods of treating cells with a trp-control agent to raise or lower the amount of biologically active trp protein and thereby control capacitative calcium ion entry into the cell. However, nothing in Birnbaumer suggests that a compound that stimulates SMCE could be used to stimulate cellular glucose uptake. Consistent with this assertion, the Office Action states at pages 3-4 that "Birnbaum et al do not specifically teach a method of determining whether a candidate agent modulates or increases capacitative calcium entry into a cell in addition to determining whether an agent modulates or increases glucose uptake into a cell or that measures glucose uptake into a cell."

Neither Draznin nor Levy, the secondary references cited in the present rejection, cure the deficiencies of Birnbaumer. In particular, nothing in these secondary references (taken alone or in combination) suggests that stimulation of SMCE will result in increased cellular glucose uptake.

Draznin discloses that although an optimal concentration of intracellular Ca^{2+} exists in adipocytes at which insulin-mediated glucose uptake can occur, increased Ca^{2+} diminishes insulin-stimulated glucose uptake (Draznin at Abstract and page 14386). Consistent with its experimental findings, Draznin states that "our recent (9) and present observations strongly suggest that high $[Ca^{2+}]_i$ may be a mechanism for deactivation or possibly termination of insulin action" (Draznin at page 14388, left column). In its conclusion, Draznin states that "[i]n obesity or in normal subjects receiving glucose/insulin infusions, increasing intracellular Ca^{2+} may result in overt insulin resistance" (Draznin at page 14388, right column).

Nothing in Draznin would have provided the person of ordinary skill in the art with the requisite suggestion or motivation to assess compounds that stimulate SMCE for their ability to increase cellular glucose uptake. In fact, Draznin actually teaches away from the currently claimed methods insofar as it states that increased calcium concentration *diminishes* insulin-stimulated glucose uptake and may trigger insulin resistance.

In addition to the foregoing, Draznin does not suggest that the experimental findings described therein occur via SMCE. Thus, not only does Draznin's disclosure regarding the

deleterious effects of high calcium concentration teach away from the claimed methods, Draznin does not suggest a role for SMCE in glucose uptake.

Levy describes intracellular calcium and its potential clinical relevance to diabetes mellitus. Levy discloses that excess or elevated calcium concentrations are hallmarks of the diabetes disease state. In particular, Levy states that "[i]ncreased intracellular calcium is the most common finding in both type 1 and type 2 diabetes [ ] as well as in obesity" (Levy at page 262, left column). Moreover, Levy states that "the density of calcium channels is increased in the leg skeletal muscle of diabetic rats," indicating that more channels and thus more Ca^{2+} influx are associated with the diabetic state (Levy at page 262, left column).

Nothing in Levy would have provided the skilled artisan with the requisite suggestion or motivation to assess compounds that stimulate SMCE for their ability to increase cellular glucose uptake. In fact, Levy, like Draznin, teaches away from the currently claimed methods insofar as it states that increased intracellular calcium is associated with diabetes and obesity.

The disclosure in each of Draznin and Levy of the deleterious effects of high calcium concentrations would have left the person of ordinary skill in the art with no reason to modify the methods of Birnbaumer so as to carry out screens to assess the ability of compounds that stimulate SMCE to increase cellular glucose uptake. Draznin and Levy would have suggested that compounds identified by such screens would, if administered to a subject, potentially result in insulin resistance and type II diabetes. As a result, applicants respectfully submit that the cited references do not render obvious amended independent claims 1, 4, or 7 or the claims that depend therefrom. Applicants request that the Examiner withdraw the rejection.

CONCLUSION

Applicants submit that all grounds for rejection have been overcome and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13425-115001.

Respectfully submitted,

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